PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
Washington, D.C.

in its capacity as elected Office

Date of mailing: 08 August 1994 (08.08.94)	
International application No.: PCT/DK94/00011	Applicant's or agent's file reference: 551
International filing date: 07 January 1994 (07.01.94)	Priority date: 15 January 1993 (15.01.93)
Applicant: HANSEN, Erik, Torngaard et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 July 1994 (07.07.94)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

C. Roy

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

To:

United States Patent and Trademark
Office
Washington, D.C.

in its capacity as elected Office

Date of mailing:
31 October 1994 (31.10.94)

International application No.:
PCT/DK94/00011

International filing date:
07 January 1994 (07.01.94)

Applicant: LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) et al

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

M. Abidine

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
551		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/DK 94/00011	07/01/1994	15/01/1993
International Patent Classification (IPC) or national classification and IPC		
C07C401/00		
Applicant		
LEO PHARMACEUTICAL PRODUCTS LTD A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and or drawings which have been amended and are the basis for this report and or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☒ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/07/1994	22.09.94
Name and mailing address of the IPEA:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	J. Mercey Telephone No.

Intern. application No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/DK94/00011

I. Basis of the report

1. This report has been drawn up on the basis of:

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[ ] the claims, No. _____, as originally filed,
No. _____, as amended under Article 19,
No. _____, filed with the demand,
No. _____, filed with the letter of _____,
No. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of: pages: _____
sheets of drawings/figures No.: _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-5	YES
	Claims	NO
Inventive Step (IS)	Claims 1-5	YES
	Claims	NO
Industrial Applicability (IA)	Claims 1-5	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

In the light of WO-A-8700834, which discloses the anhydrous form of calcipotriol, the problem to be solved by the present invention may be regarded as the provision of a form of calcipotriol which is more suitable for formulation into pharmaceutical compositions.

The solution provided by claim 1, namely the **monohydrate** of calcipotriol, is more stable then the anhydrous form and is technically superior in the manufacture of crystal suspension formulations (being easily wetted and the wet ball milling process runs smoothly). These improvements could not have been expected in the light of either WO-A-8700834, or any of the other cited art, none of which suggests a hydrated form of calcipotriol.

Hence claim 1 (the monohydrate *per se*) and claims 2 to 5 (pharmaceutical compositions containing it) fulfil the requirements of Articles 33(2) and (3) PCT.

VI. Certain documents cited

1. Certain published documents

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)

Larsen et al., Acta Crystallogr., Sect. C: Cryst. Struct. Commun.; 1993; Vol. C49 (3); pp. 618-621

2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

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Name and mailing address of the IPEA/	Authorized officer
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Intern. application No.

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Larsen et al., Acta Crystallogr., Sect. C: Cryst. Struct. Commun.; 1993; Vol. C49 (3); pp. 618-621

2. Non-written disclosures

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 94/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C401/00 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,87 00834 (LEO PHARMACEUTICAL PRODUCTS LTD) 12 February 1987 cited in the application see page 12; examples 58,59 see page 40 - page 42; examples 3-7 ---	1-5
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. vol. 171, no. 3 , 28 September 1990 , DULUTH, MINNESOTA US pages 1056 - 1063 M. THAVARAJAH ET AL '1,25(OH)2D3 and Calcipotriol (MC903) Have Similar Effects on The Induction of Osteoclast-Like Cell Formation in Human Bone Marrow Cultures' see the whole document --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 1994	25.04.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993, Columbus, Ohio, US; abstract no. 41719, M. BAGOT ET AL 'Immunosuppressive Effects of 1,25-Dihydroxyvitamin D3 Analog (Calcipotriol) on Epidermal Cells' page 182 ;column 1 ; see abstract & PROC. WORKSHOP VITAM. D (8TH) 1991 pages 518 - 519 ---	1-5
A	CHEMICAL ABSTRACTS, vol. 117, no. 21, 23 November 1992, Columbus, Ohio, US; abstract no. 205159, M. BRAEUTIGAM ET AL 'Effects of Calcipotriol (MC903) and Calcitriol After Topical Application on The Skin of Hairless Rats. Much Lower Effect of Calcipotriol on Systemic Calcium Homeostasis' page 93 ;column 1 ; see abstract & SKIN PHARMACOL. vol. 5, no. 2 , 1992 pages 87 - 92 ---	1-5
A	CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992, Columbus, Ohio, US; abstract no. 248622, K. KRAGBALLE ET AL 'Vitamin D Analogs in The Treatment of Psoriasis.' page 90 ;column 1 ; see abstract & J. CELL. BIOCHEM. vol. 49, no. 1 , 1992 pages 46 - 52 ---	1-5
P,X	ACTA CRYSTALLOGRAPHICA . SECTION C, CRYSTAL STRUCTURE COMMUNICATIONS vol. C49, no. 3 , 1993 , COPENHAGEN, DK pages 618 - 621 S. LARSEN ET AL 'Structure and Absolute Configuration of a Monohydrate of Calcipotriol, (1.alpha.,3 ,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol' see the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/DK 94/00011

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8700834	12-02-87	AU-B-	603340	15-11-90
		AU-A-	6196186	05-03-87
		EP-A,B	0227826	08-07-87
		JP-T-	63500661	10-03-88
		US-A-	4866048	12-09-89

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 401/00, A61K 31/59

A1

(11) International Publication Number: WO 94/15912

(43) International Publication Date: 21 July 1994 (21.07.94)

(21) International Application Number: PCT/DK94/00011

(22) International Filing Date: 7 January 1994 (07.01.94)

(30) Priority Data:
9300763.1 15 January 1993 (15.01.93) GB

(71) Applicant *(for all designated States except US)*: LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HANSEN, Erik, Torngaard [DK/DK]; Asmundshøj 457, DK-3480 Fredensborg (DK). RASTRUP ANDERSEN, Niels, Smidt [DK/DK]; Tyborøn Allé 68, DK-2720 Vanløse (DK). RINGBORG, Lene, Hoffmeyer [DK/DK]; Toftagervej 27, DK-2700 Brønshøj (DK).

(74) Agent: KRISTENSEN, Per, Rydahl; Leo Pharmaceutical Products Ltd. A/S (Løvens Kemiske Fabrik), Patent Department, Industriparken 55, DK-2750 Ballerup (DK).

(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW CRYSTALLINE FORM OF A VITAMIN D ANALOGUE

(57) Abstract

The present invention relates to calcipotriol hydrate - a new crystalline form of calcipotriol - with superior technical properties and with superior stability.

NEW CRYSTALLINE FORM OF A VITAMIN D ANALOGUE

The present invention relates to calcipotriol, hydrate - a new crystalline form of calcipotriol - with superior technical properties e.g. in the manufacture of crystal suspension formulations, and with superior stability properties.

Calcipotriol (INN) (calcipotriene (USAN), (1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,-10(19),22-tetraene-1,3,24-triol) is described in International patent application No. PCT/DK86/00081, filing date 14th July 1986, publication No. WO 87/00834.

Calcipotriol possesses a remarkable profile of biological activity which has proved very useful e.g. in the topical treatment of psoriasis.

Due to the poor stability of calcipotriol in certain solutions it is in some formulations, in particular in creams and gels, preferred to use crystal suspensions.

In order to prepare suitable crystal suspension formulations it is mandatory to be able to control the crystal size, this parameter being important with regard to obtaining a reproducible release of the active compound from the formulation. The crystalline bulk drug is usually subjected to micronization or to a wet milling process in order to reduce the crystal size before the final suspension formulation is prepared.

In the case of calcipotriol a wet ball milling process has been used. However, it has turned out to be technically difficult to perform this process when using the anhydrous crystal form described in WO 87/00834. These crystals are not easily wetted and during the milling process they develop a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

It has now surprisingly been found that these technical problems can be avoided when a hitherto unknown cry-

stalline form of calcipotriol, i.e. calcipotriol, hydrate, is used instead of the known anhydrous form. The hydrate is technically superior to the anhydrate; it is easily wetted and the wet ball milling process is running smoothly.

This novel product is the monohydrate of calcipotriol which is perfectly crystalline, stable and well suited for its use in modern therapy.

Stability studies have demonstrated that calcipotriol, hydrate is surprisingly stable, and this is illustrated by stability data at 40°C.

The anhydrous form of calcipotriol shows a considerable degree of decomposition at this temperature and more than 30% degradation is seen after 12 months storage.

In contrast the compound of the present invention, calcipotriol hydrate, shows no degradation after 12 months storage at 40°C.

Calcipotriol, monohydrate may be prepared by dissolving crystalline or non-crystalline calcipotriol in an organic solvent, e.g. ethyl acetate or acetone, followed by the addition of water and optionally a non polar solvent, e.g. hexane.

Calcipotriol, monohydrate shall form part of pharmaceutical preparations for topical use, such as creams, ointments, solutions, lotions or gels. The concentration of the active ingredient will generally be between 1 and 100 µg/g.

The formulations will be applied one or more times daily.

The formulations prepared according to the present invention comprise the active compound in association with a pharmaceutically acceptable vehicle and optionally other therapeutic ingredient(s). The vehicle(s) must be "acceptable" in the sense of being compatible with the other ingredients of the preparations and not deleterious to the recipient thereof.

Preparations suitable for topical administration include liquid or semi-liquid preparations such as lini-

ments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, pastes or gels; or solutions or suspensions.

In addition to the aforementioned ingredients, the preparations of this invention may include one or more additional ingredients such as diluents, buffers, surface active agents, thickeners, lubricants, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

The invention will now be further described in the following non-limiting Examples:

Example 1

Calcipotriol (2.5 g) was dissolved in ethyl acetate (80 ml) at 50-80°C and filtered. The solution was saturated with water, and the product precipitated upon voluntary cooling to room temperature. The resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to give calcipotriol, hydrate (2.35 g).

IR spectroscopy KBr technique

Lines characteristic for the hydrate are 1455 (m), 1442 (m), 1330 (w), 1290 (m), 1210 (m), 1085 (m), 907 (m), 895 (m) and 573 (w) cm^{-1}, respectively.

Solid state CPMAS[1] NMR

The following resonances are characteristic for calcipotriol, hydrate: 147.9, 146.5, 134.8, 130.3, 129.0, 126.5, 116.0, 109.4, 75.5, 68.2, 67.2, 56.9, 55.2, 47.8, 47.5, 42.9, 42.0, 41.3, 30.7, 28.9, 25.6, 23.1, 22.6, 19.5, 14.6, 6.2 and 1.9 ppm, respectively.

Differential Scanning Calorimetry (DSC)

On a Perkin Elmer DSC7 instrument using 20°C/min. and approx. 2 mg sample, the hydrate shows loss of water near 117°C and a melting peak near 169.7°C.

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[1] Cross Polarization Magic Angle Spinning

Example 2

Calcipotriol (22.7 g) was dissolved in methanol (200-250 ml), filtered and concentrated in vacuo to a residue which was dissolved in ethyl acetate (200-250 ml) at 50-80°C and water (2 ml) was added. The resulting solution was seeded with calcipotriol, hydrate, and the product precipitated upon voluntary cooling to room temperature. Hexane (100 ml) was added from a dropping funnel, the resulting slurry was cooled to 0-10°C and filtered.

The filtered product was washed with a 1:1 mixture of ethyl acetate and hexane (200 ml) and dried in vacuo to give calcipotriol, hydrate (19.7 g), shown to be identical with the product described in Example 1.

Example 3

Calcipotriol (120 mg) was dissolved in acetone (2 ml) and water (1.5-3 ml) was added. The product crystallized spontaneously and the resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to yield calcipotriol, hydrate (100 mg), shown to be identical with the product of Example 1.

Example 4

Cream 50 µg/g

Calcipotriol, hydrate	50 mg
Cetomacrogol 1000	30 g
Cetostearylalcohol	60 g
Chloroallylhexaminium chloride	0.5 g
Propyleneglycol	30 g
Disodiumhydrogenphosphate	2 g
Liquid paraffin	50 g
White soft paraffin	170 g
Purified water ..... up to	1000 g

Melt cetomacrogol 1000, cetostearylalcohol, liquid paraffin and white soft paraffin at 75°C. Dissolve propylene glycol in water at 75°C and mix the solution with the fatty phase. Homogenize the emulsion and cool to 30°C. Mill calcipotriol, hydrate in part of the aqueous phase to a particle size predominantly below 10 µm and suspend in an aqueous solution of disodiumhydrogenphosphate and chloroallylhexaminiumchloride. Add the suspension to the emulsion and fill the cream in tubes.

Example 5

Gel 50 µg/g

Calcipotriol, hydrate		52.2 mg
(corresponding to 50 mg anhydrous)		
Carbomer		7 g
Cetomacrogol 1000		1 g
Diazolidinyl urea		2 g
Dichlorobenzyl alcohol		1 g
Disodium edetate		0.5 g
Sodium hydroxide		3.7 g
Propylene glycol		30 g
Purified water	up to	1000 g

Dissolve cetomacrogol, diazolidinyl urea, dichlorobenzyl alcohol, disodium edetate and propylene glycol in water. Add carbomer and homogenize by high speed. Add during agitation sodium hydroxide dissolved in part of the water. Mill the calcipotriol, hydrate in a bottle of water with glass beads until a particle size below 10 µm has been obtained. Add the calcipotriol, hydrate suspension to the gel and mix for 30 minutes. Fill the gel into collapsible tubes.

WHAT WE CLAIM IS:

1. Calcipotriol [2], monohydrate.

2. Pharmaceutical composition containing the compound of claim 1.

3. Pharmaceutical composition according to claim 2 which is a cream.

4. Pharmaceutical composition according to claim 2 which is a gel.

5. Pharmaceutical composition according to any one of claims 2 - 4, with a content of the active component of 1 - 100 μg/g of the composition.

---

[2] 1α,3β,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 94/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C401/00 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 1994	25. 04. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Watchorn, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993, Columbus, Ohio, US; abstract no. 41719, M. BAGOT ET AL 'Immunosuppressive Effects of 1,25-Dihydroxyvitamin D3 Analog (Calcipotriol) on Epidermal Cells' page 182 ;column 1 ; see abstract & PROC. WORKSHOP VITAM. D (8TH) 1991 pages 518 - 519 ---	1-5
A	CHEMICAL ABSTRACTS, vol. 117, no. 21, 23 November 1992, Columbus, Ohio, US; abstract no. 205159, M. BRAEUTIGAM ET AL 'Effects of Calcipotriol (MC903) and Calcitriol After Topical Application on The Skin of Hairless Rats. Much Lower Effect of Calcipotriol on Systemic Calcium Homeostasis' page 93 ;column 1 ; see abstract & SKIN PHARMACOL. vol. 5, no. 2 , 1992 pages 87 - 92 ---	1-5
A	CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992, Columbus, Ohio, US; abstract no. 248622, K. KRAGBALLE ET AL 'Vitamin D Analogs in The Treatment of Psoriasis.' page 90 ;column 1 ; see abstract & J. CELL. BIOCHEM. vol. 49, no. 1 , 1992 pages 46 - 52 ---	1-5
P,X	ACTA CRYSTALLOGRAPHICA . SECTION C, CRYSTAL STRUCTURE COMMUNICATIONS vol. C49, no. 3 , 1993 , COPENHAGEN, DK pages 618 - 621 S. LARSEN ET AL 'Structure and Absolute Configuration of a Monohydrate of Calcipotriol, (1.alpha.,3 ,5Z,7E,22E,24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol' see the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 94/00011

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8700834	12-02-87	AU-B-	603340	15-11-90
		AU-A-	6196186	05-03-87
		EP-A,B	0227826	08-07-87
		JP-T-	63500661	10-03-88
		US-A-	4866048	12-09-89

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
551		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/DK94/00011	07/01/94	15/01/93
Applicant		
LEO PHARMACEUTICAL PRODUCTS LTD A/S et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 94/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C401/00 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,87 00834 (LEO PHARMACEUTICAL PRODUCTS LTD) 12 February 1987 cited in the application see page 12; examples 58,59 see page 40 - page 42; examples 3-7 ---	1-5
A	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. vol. 171, no. 3 , 28 September 1990 , DULUTH, MINNESOTA US pages 1056 - 1063 M. THAVARAJAH ET AL '1,25(OH)2D3 and Calcipotriol (MC903) Have Similar Effects on The Induction of Osteoclast-Like Cell Formation in Human Bone Marrow Cultures' see the whole document --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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